

DISRUPTIVE THERAPIES

BARDA INDUSTRY DAY

October 30, 2018

Martine Rothblatt, PhD, JD

CEO and Founder, United Therapeutics Corporation



SAFE HARBOR STATEMENT

Remarks today concerning

United Therapeutics may include forward-looking statements which represent United Therapeutics’ expectations or beliefs regarding future events. We caution that such statements involve risks and uncertainties that may cause actual results to differ materially from those in the forward-looking statements. Consequently, all such forward-looking statements are qualified by the cautionary language and risk factors set forth in United Therapeutics’ periodic and other reports filed with the SEC.

There can be no assurance

that the actual results, events or developments referenced in such forward-looking statements will occur or be realized. United Therapeutics assumes no obligation to update these forward-looking statements to reflect actual results, changes in assumptions or changes in factors affecting such forward-looking statements.

This presentation

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UT FACTS



Focus

Advance

Create

Transform

FOCUSED ON OUR PATIENTS

Commercial Products

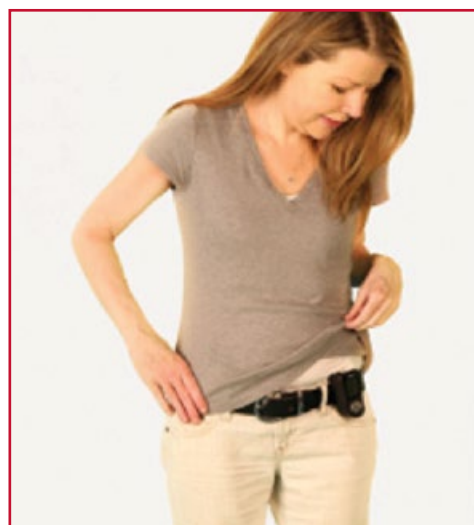
PULMONARY ARTERIAL HYPERTENSION (PAH)


orenitram[®]
treprostinil
EXTENDED-RELEASE TABLETS



TABLET


REMODULIN[®]
(treprostinil) Injection



INFUSION

TYVASO[®]
(treprostinil) INHALATION
SOLUTION



INHALATION

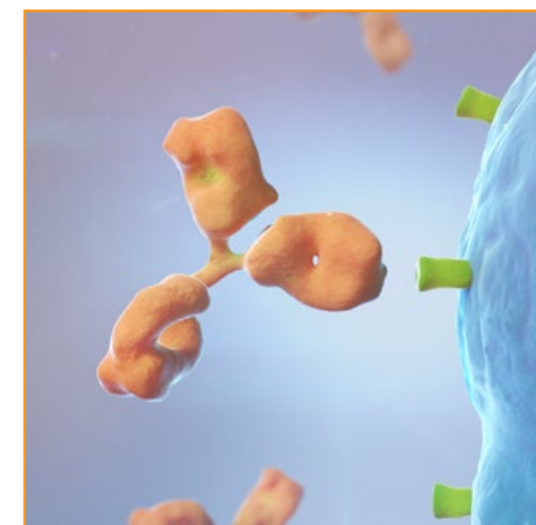

adcirca[®]
tadalafil tablets 20mg



TABLET

ONCOLOGY

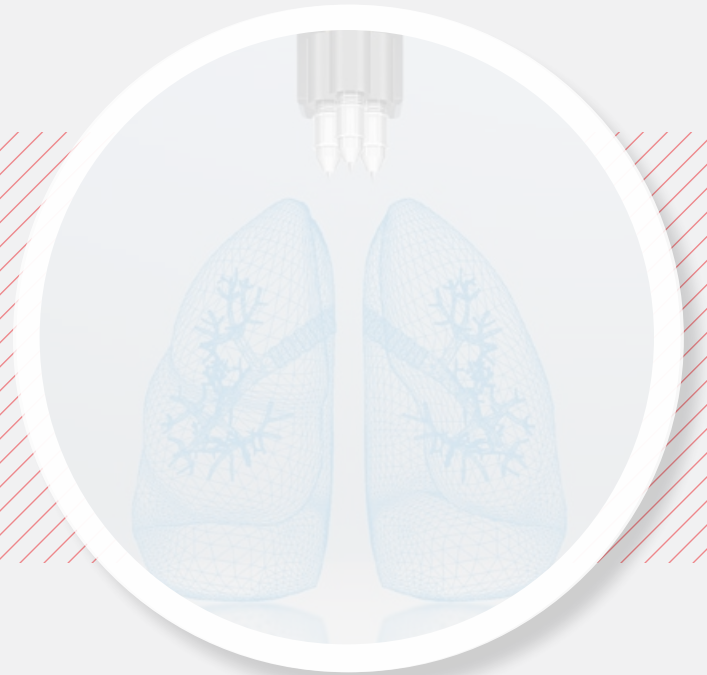
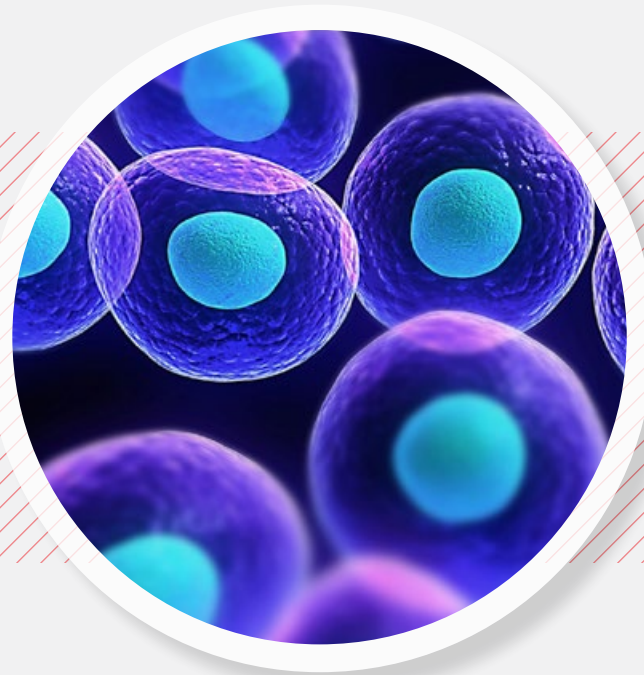

Unituxin[®]
(dinutuximab)
Injection



INJECTION



UT FACTS



Focus

Advance

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Transform



ADVANCE AUTONOMOUS DRUG DELIVERY FOR MASS CASUALTY CARE

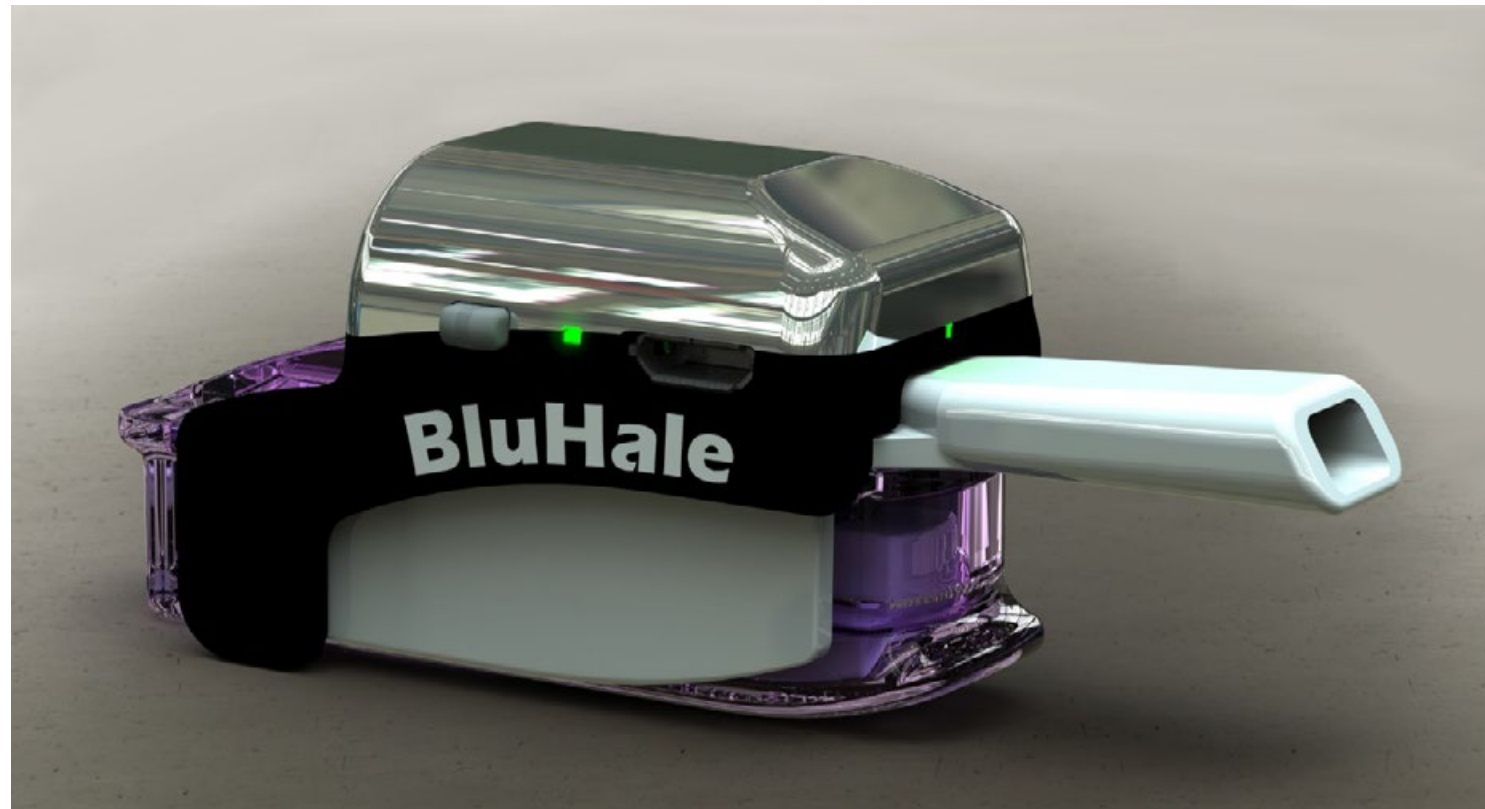
 PatchPump®



- » Example: Implantable Remodulin is FDA-approved
- » Transforms any limited use short $T^{1/2}$ drug or biologic into a clinically viable therapy
- » Patch pump safely applied by rescuer; appropriate for *steady state* antibiotics, naloxone (weaponized opiate) or atropine (chemical weapons)



ADVANCE NOVEL SYNERGISTIC THERAPIES

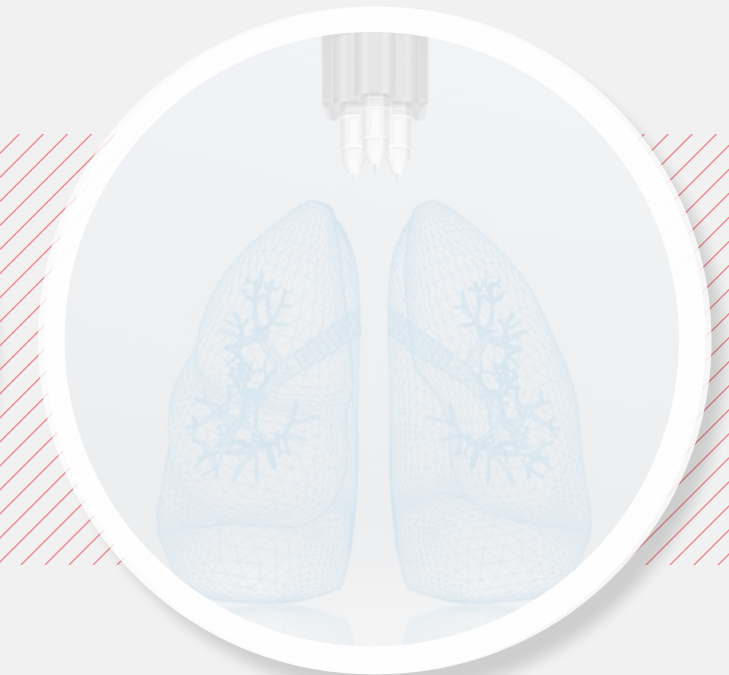
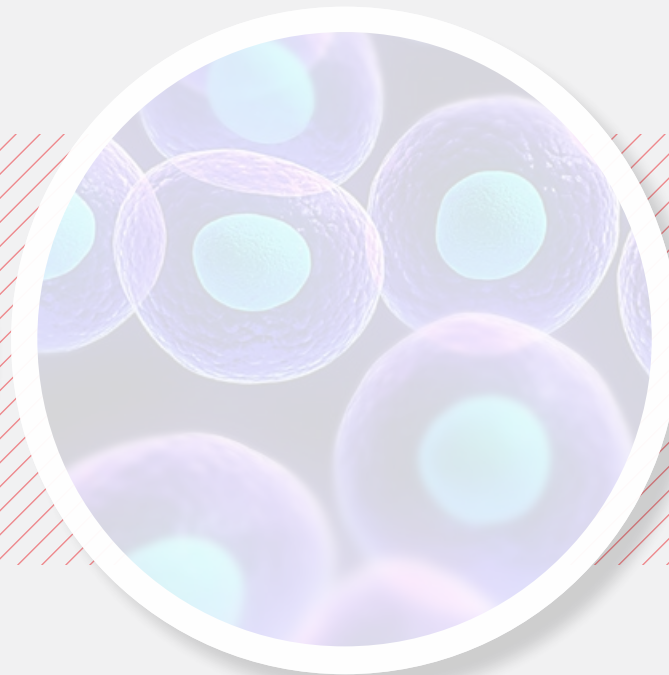


- » Treprostinil in next generation inhaler
- » Multiple therapies in SNS can have route, spectrum and PK expanded for mass casualty care

SNS=Strategic National Stockpile



UT FACTS



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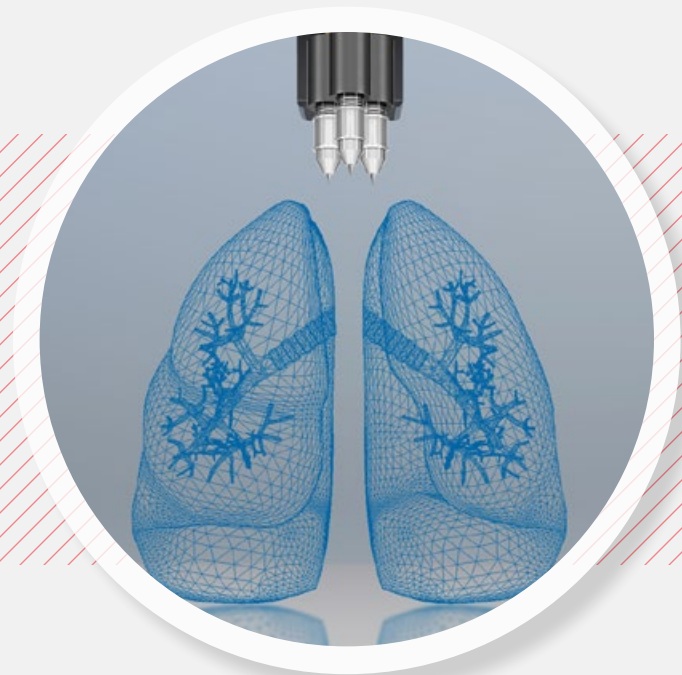
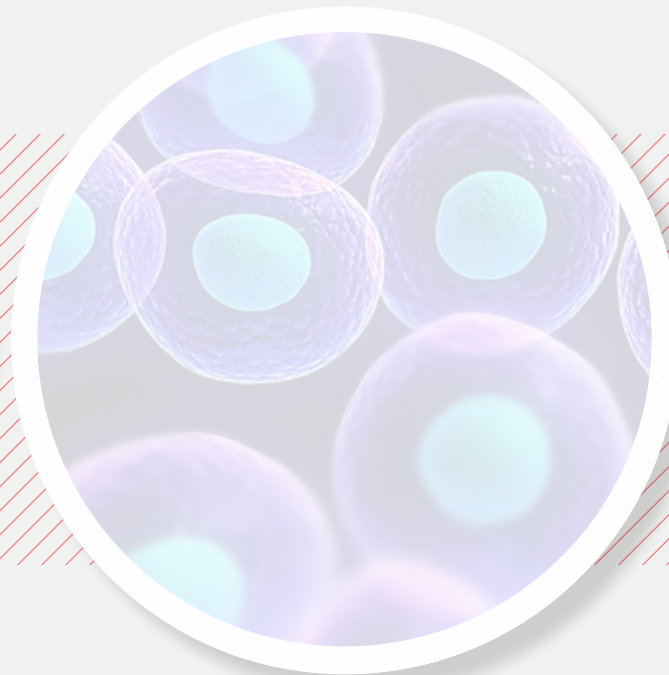
INCREASE CLINICAL TRIAL IN PH WHO GROUP 3

- » Example: (1) Inhaled treprostinil (PAH) adapted to ILD; (2) use NSAIDs to boost NAI plasma levels in severe flu
- » UT aero-medicinals deliver to precise regions of lung (80nm-100um)
- » Novel biologics (mAB) cellular and adenoviral therapy given as aerosols





UT FACTS



Focus

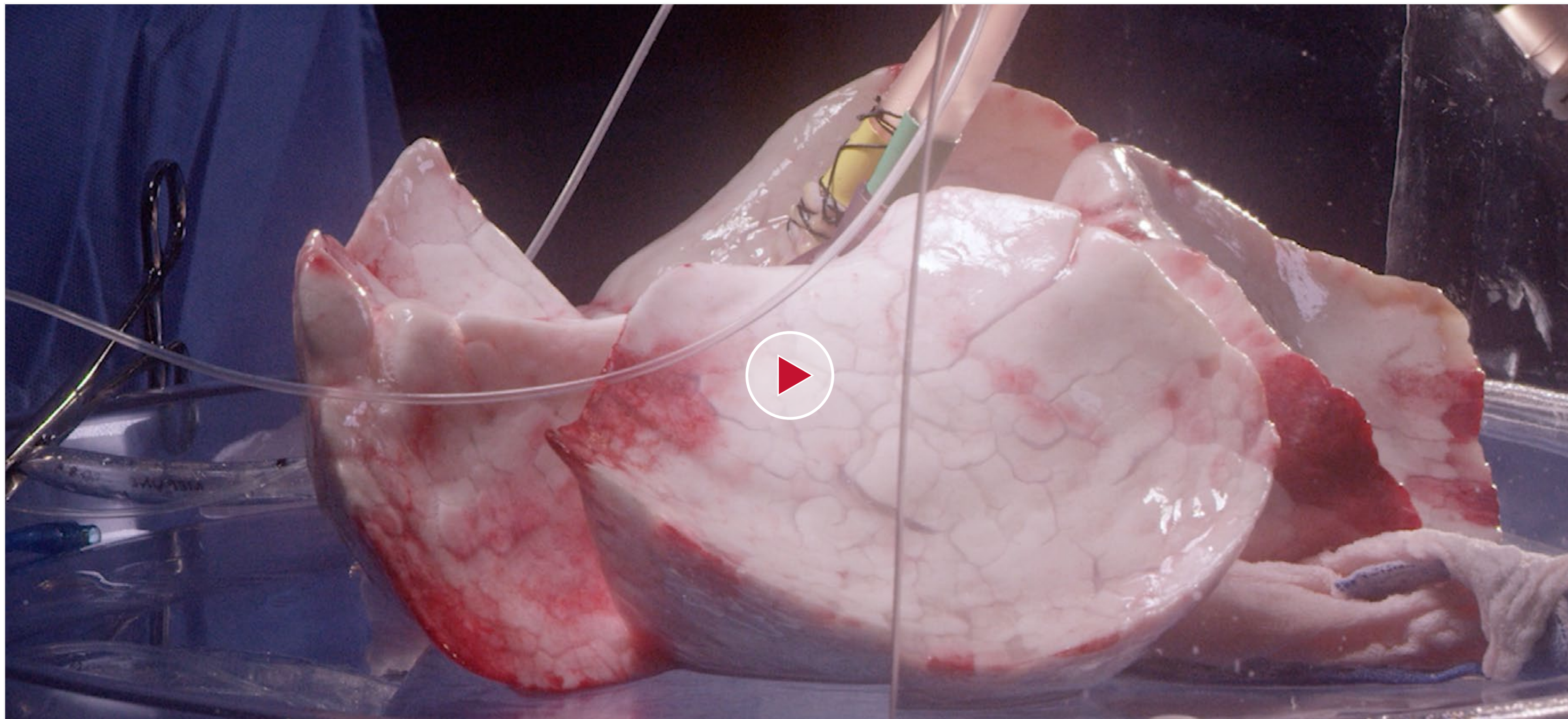
Advance

Create

Transform



EVLP





WORLDWIDE EVLP PATIENTS TO DATE

1636 LIVES SAVED*

*Global figure including all EVLP technologies. To date, our EVLP clinical trial has successfully transplanted EVLP lungs into more than 50 patients.



UNITED THERAPEUTICS LUNG RECIPIENTS



HEATHER LEVERINGTON



20 months post double lung transplant, Heather won two gold medals at the 2018 US Transplant Games in Utah.



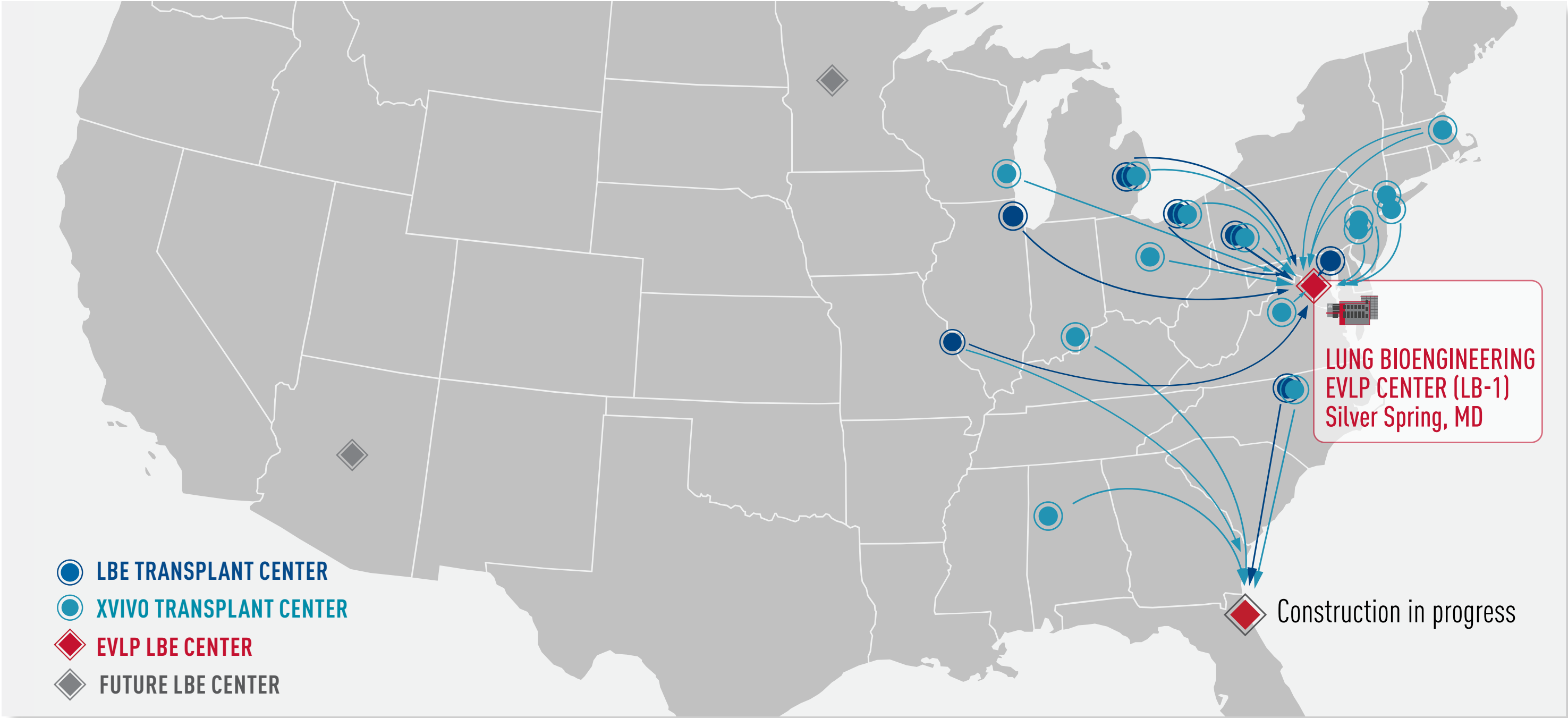
CHUCK BOETSCH



I did my first 5k in early May, and this was my second. I have also traveled to Colorado, up to 10,500 feet with no issues.

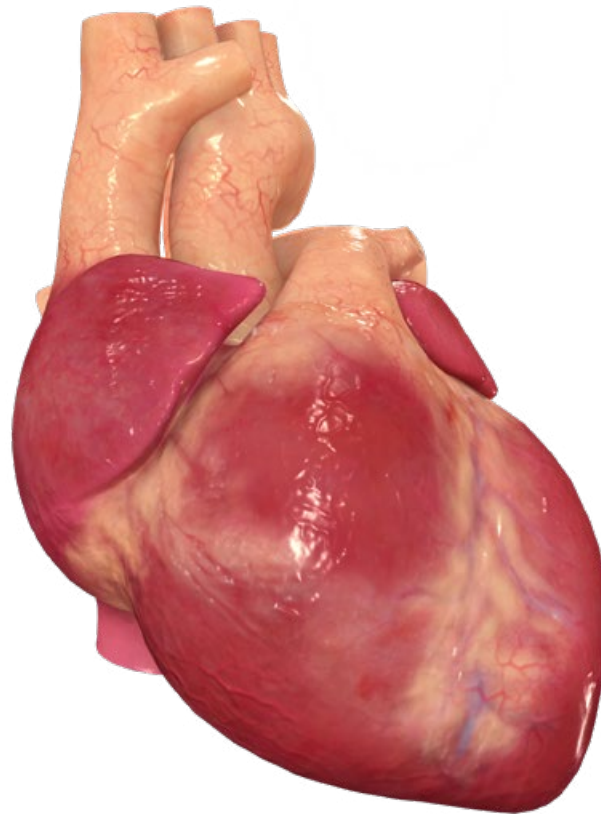
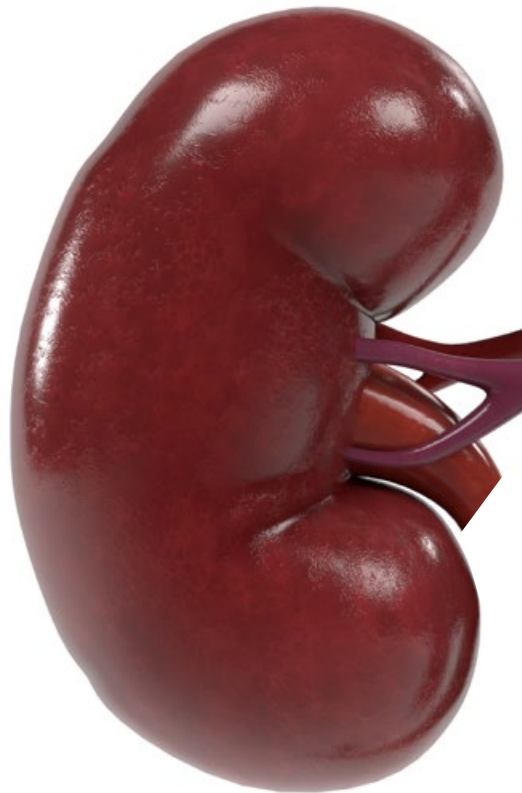


UT LUNG SERVICE MODEL



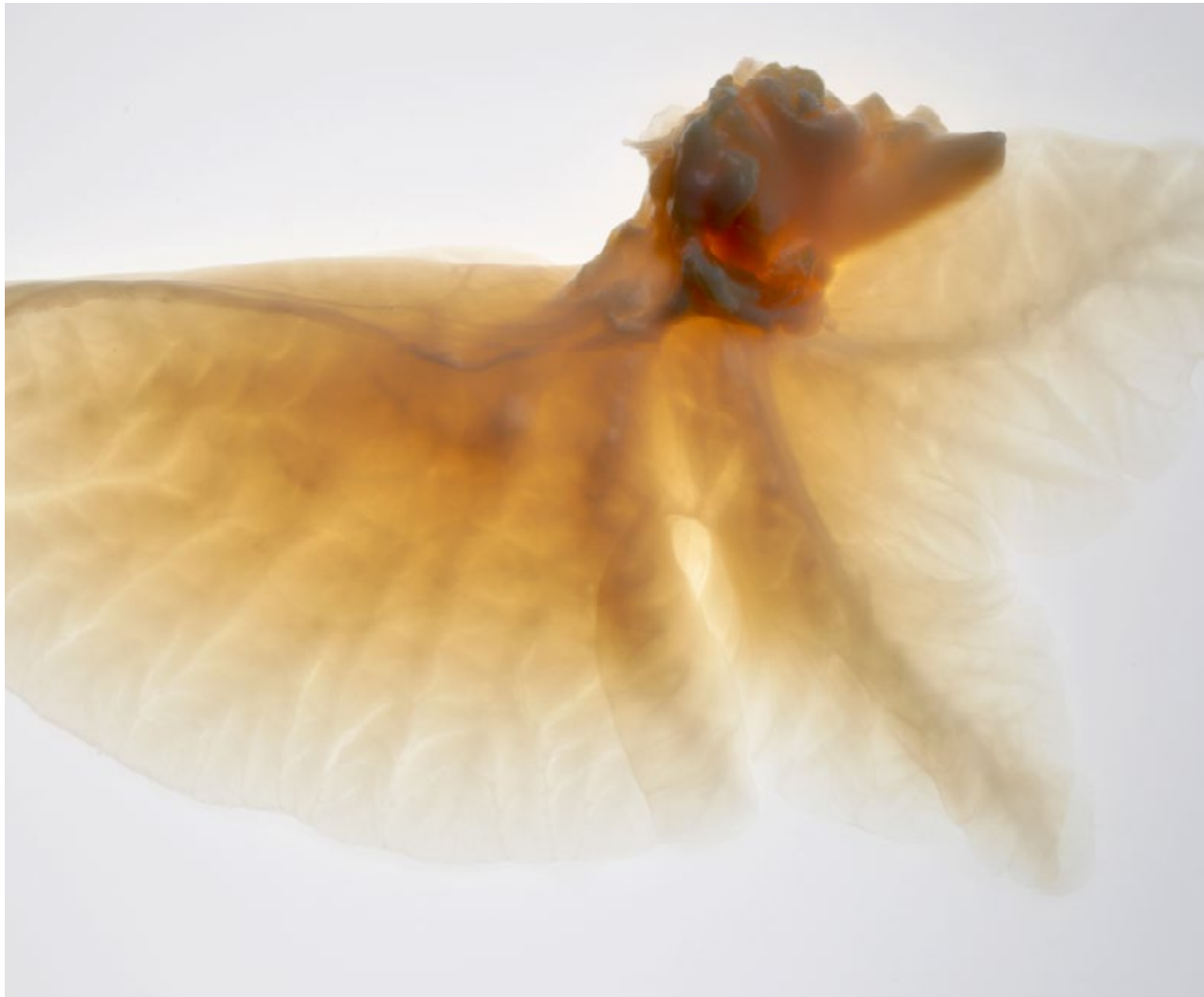


EX-VIVO ORGAN PERFUSION EXPANSION MODEL





LONGER TERM VISION DE NOVO LUNGS + CELLULARIZATION





DOUBLE / TRIPLE SUPPLY





3D BIO PRINTING

Organ
Manufacturing





CELL THERAPY¹

How cell therapy works?

EXAMPLE

Restoring nitric oxide enzyme in PAH patients using their cells

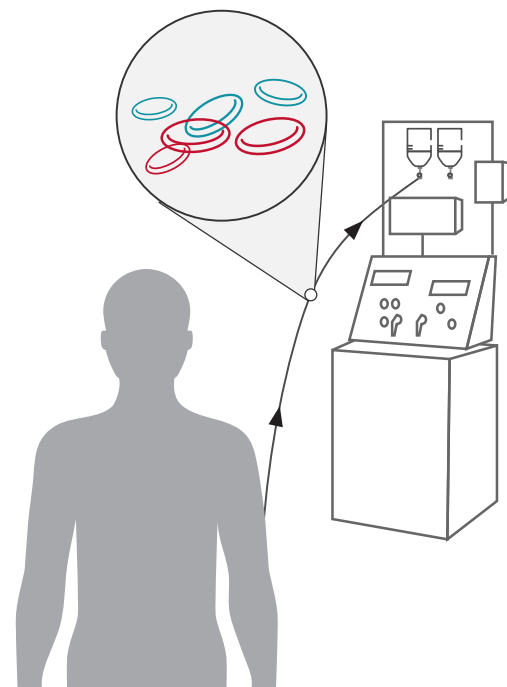
 Endothelial progenitor cells (EPCs)

 eNOS gene

 Cell expansion

 Transfection

ISOLATE EPCs FROM
PATIENT (DAY 0)



LEUKAPHERESIS

1. Adapted from Callahan et. Al. *Severe Immune Complication Committee (SICC), MGH and the U.U. FDA*



CELL THERAPY¹

How cell therapy works?

EXAMPLE
Restoring nitric oxide enzyme in PAH patients using their cells

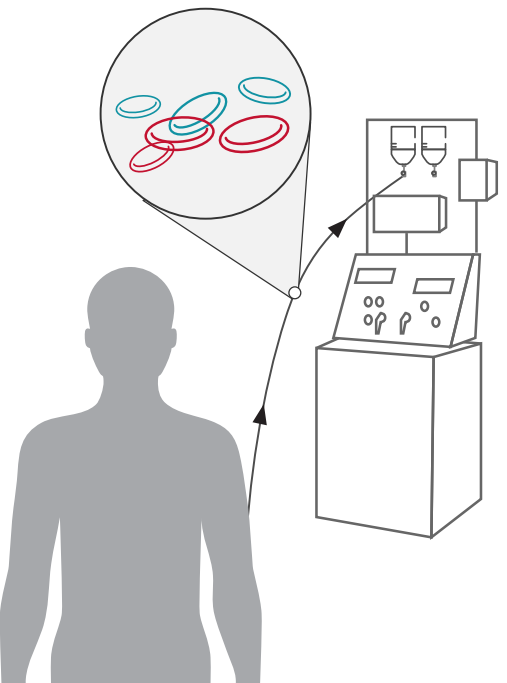
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 eNOS gene

 Cell expansion

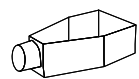
 Transfection

ISOLATE EPCs FROM PATIENT (DAY 0)



LEUKAPHERESIS

1



XPAND EPCS 2000X



MANUFACTURING PROCESS

1. Adapted from Callahan et. Al. *Severe Immune Complication Committee (SICC), MGH and the U.U. FDA*



CELL THERAPY¹

How cell therapy works?

EXAMPLE
Restoring nitric oxide enzyme in PAH patients using their cells

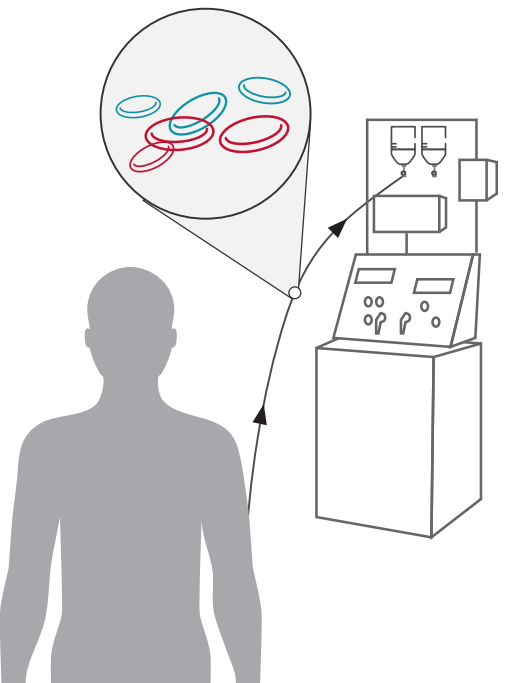
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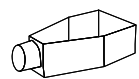
 Transfection

ISOLATE EPCs FROM PATIENT (DAY 0)



LEUKAPHERESIS

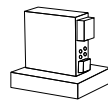
1



XPAND EPCS 2000X



2



TRANSFECT WITH ENOS GENE



(DAY 1-26)

MANUFACTURING PROCESS

1. Adapted from Callahan et. AL. *Severe Immune Complication Committee (SICC), MGH and the U.U. FDA*



CELL THERAPY¹

How cell therapy works?

EXAMPLE
Restoring nitric oxide enzyme in PAH patients using their cells

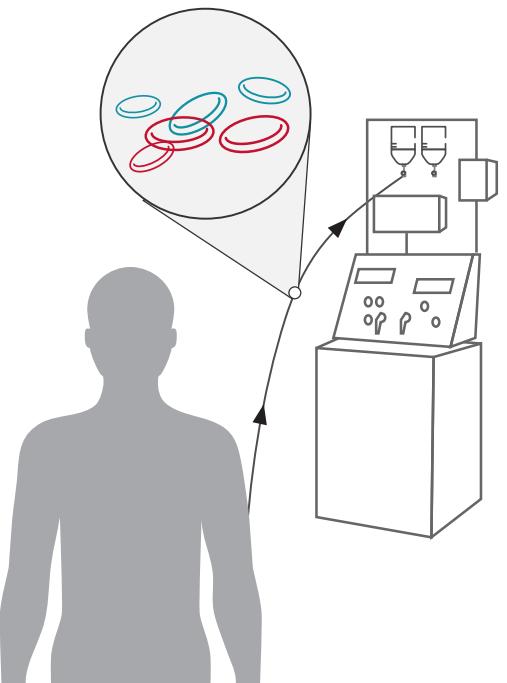
 Endothelial progenitor cells (EPCs)

 eNOS gene

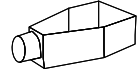
 Cell expansion

 Transfection

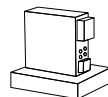
ISOLATE EPCs FROM PATIENT (DAY 0)

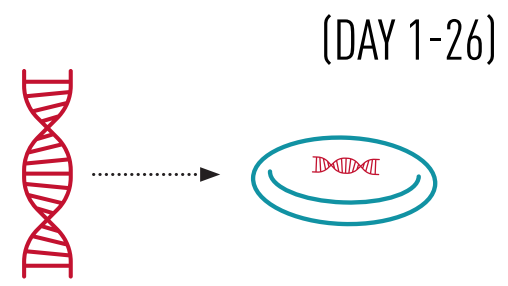


LEUKAPHERESIS

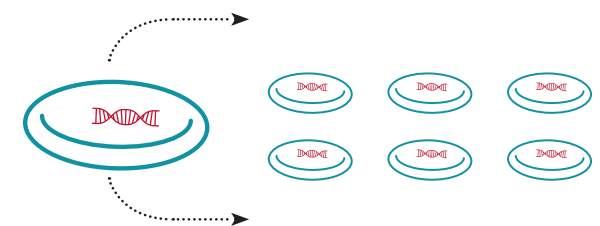
1  XPAND EPCS 2000X



2  TRANSFECT WITH ENOS GENE



3 FREEZE CELLS FOR FUTURE USE



MANUFACTURING PROCESS

1. Adapted from Callahan et. Al. *Severe Immune Complication Committee (SICC), MGH and the U.U. FDA*



UT CELL THERAPY¹


How cell therapy works?

EXAMPLE

Sapphire: restore nitric oxide enzyme in PAH patients

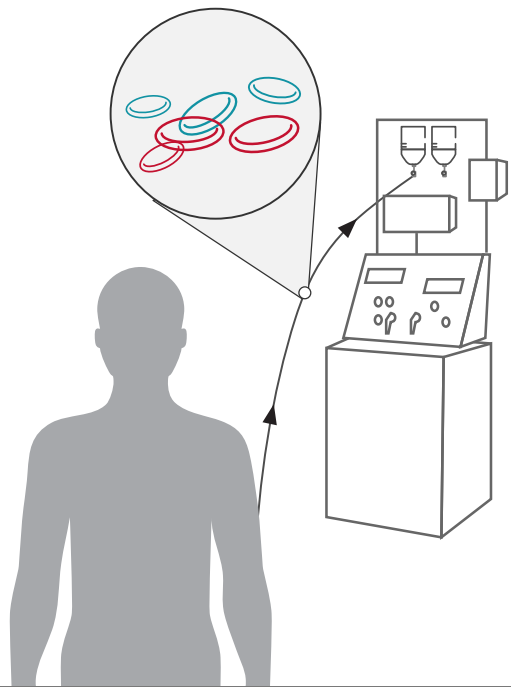
 Endothelial progenitor cells (EPCs)

 eNOS gene

 Cell expansion

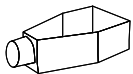
 Transfection

ISOLATE EPCs FROM
PATIENT (DAY 0)



LEUKAPHERESIS

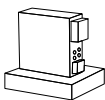
1



XPAND EPCS 2000X



2



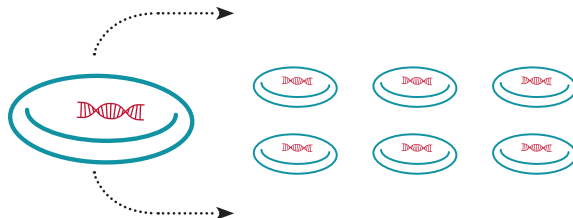
TRANSFECT WITH
ENOS GENE



(DAY 1-26)

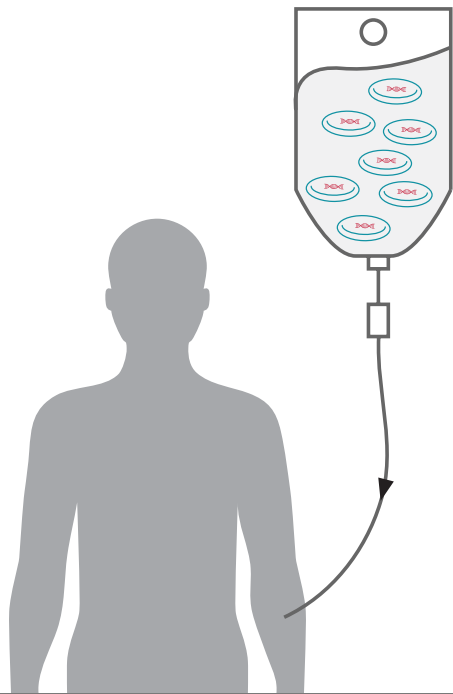
3

FREEZE CELLS
FOR FUTURE USE



MANUFACTURING PROCESS

DELIVER MONTHLY
DOSES IV



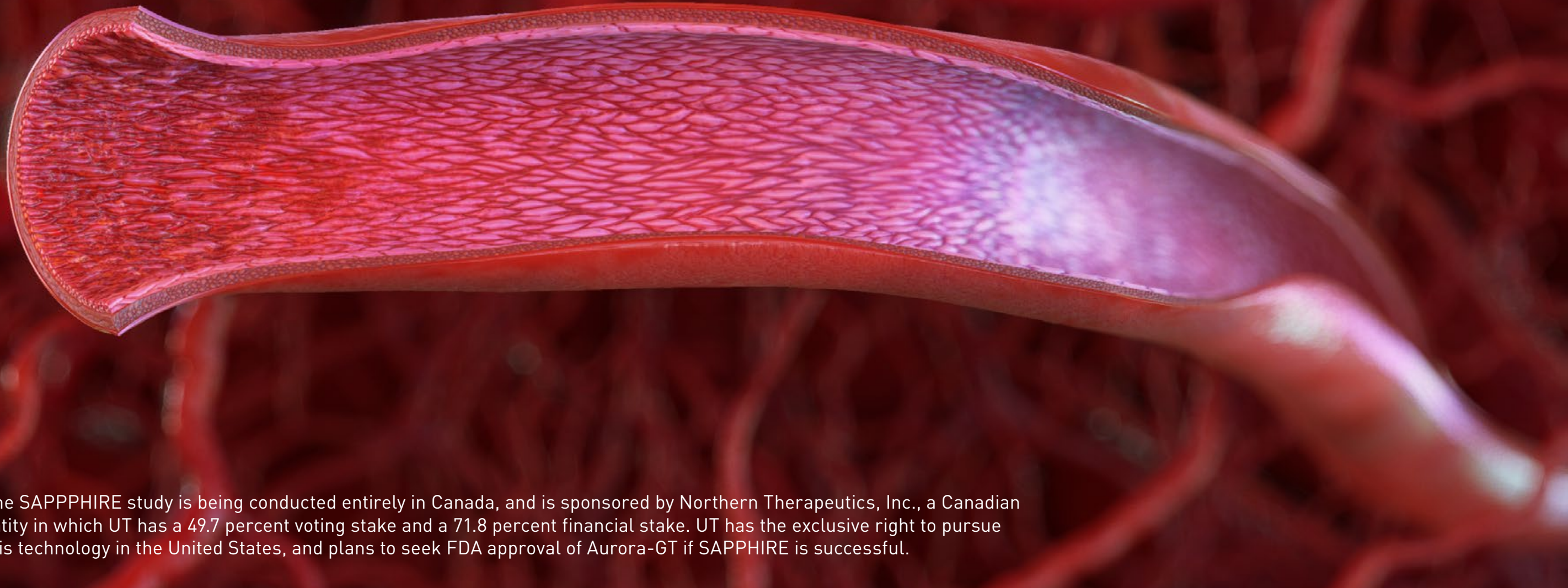
INFUSION

1. Adapted from Callahan et. Al. *Severe Immune Complication Committee (SICC), MGH and the EMA/SFDA*



SAPPHIRE STUDY*

Study of **A**ngiogenic Cell Therapy for **P**rogressive **P**ulmonary **H**ypertension: **I**ntervention With **R**epet Dosing of eNOS-enhanced **E**PCs

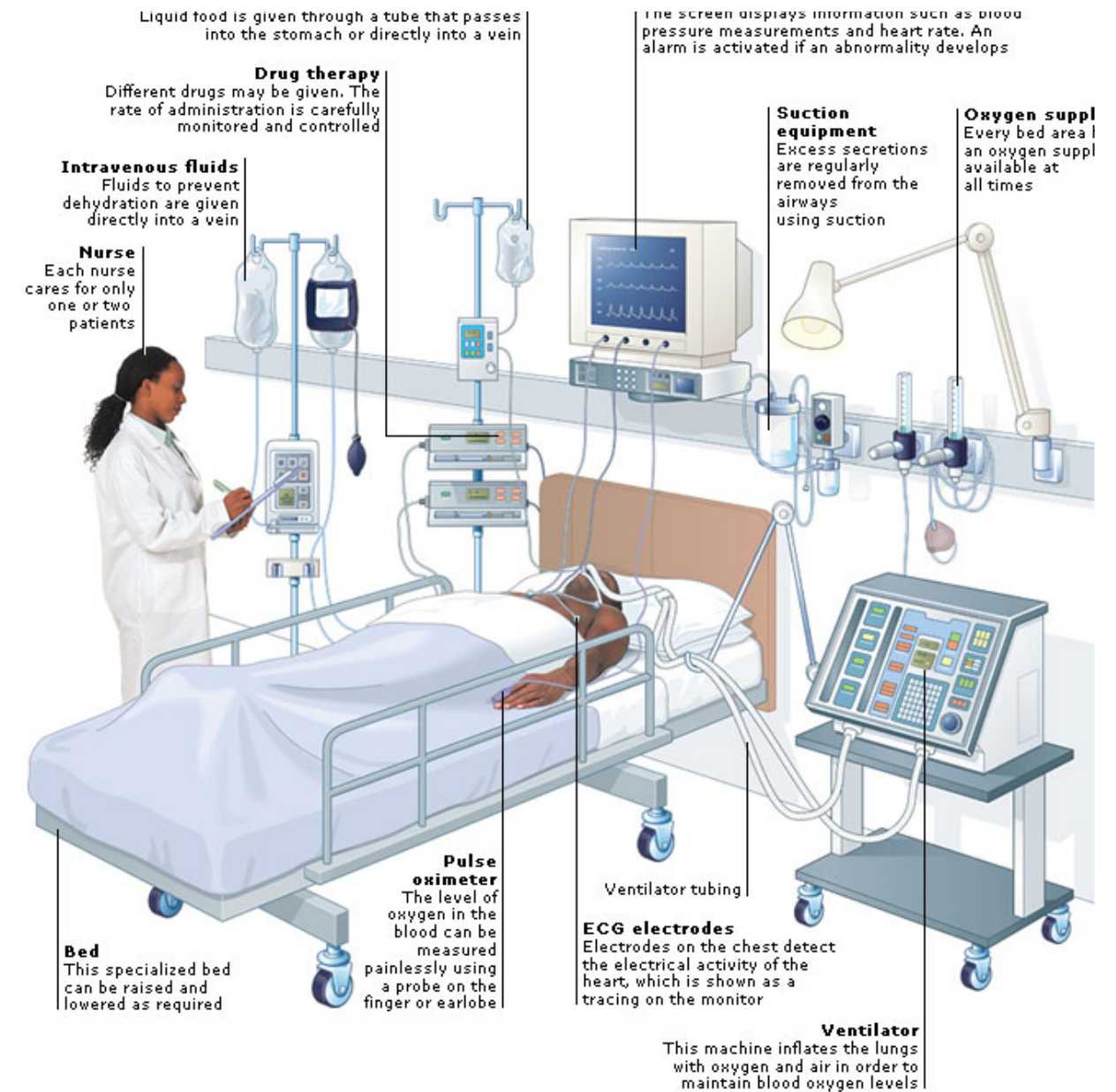


*The SAPPHIRE study is being conducted entirely in Canada, and is sponsored by Northern Therapeutics, Inc., a Canadian entity in which UT has a 49.7 percent voting stake and a 71.8 percent financial stake. UT has the exclusive right to pursue this technology in the United States, and plans to seek FDA approval of Aurora-GT if SAPPHIRE is successful.



SEPSIS TPP

Cellular therapies, given intravenously provide an opportunity to transfer beneficial responses observed in sepsis survivors. The code book for sepsis survival can be encoded in a multipurpose, long lived, cryopreserved product





SEPSIS IN THE US

OVER 1.7M CASES⁽¹⁾ AND 265,000 DEATHS IN US PER YEAR⁽²⁾

SEPSIS IN THE U.S. IS INCREASING

- » Aging population and increased immune-suppressed population
- » Imported and domestic pan-resistant bacteria
- » 1 patient dies every 2 minutes from sepsis

1. Hershey TB; NEJM, 2017 2. Rhee, C; JAMA, 2017



AT LEAST 250,000 AMERICANS DIE FROM SEPSIS EACH YEAR.


**GET AHEAD
OF SEPSIS**



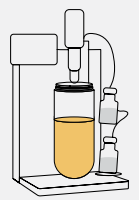


A UNIVERSAL CELL THERAPY FOR SEPSIS


Aurora GT




Vial



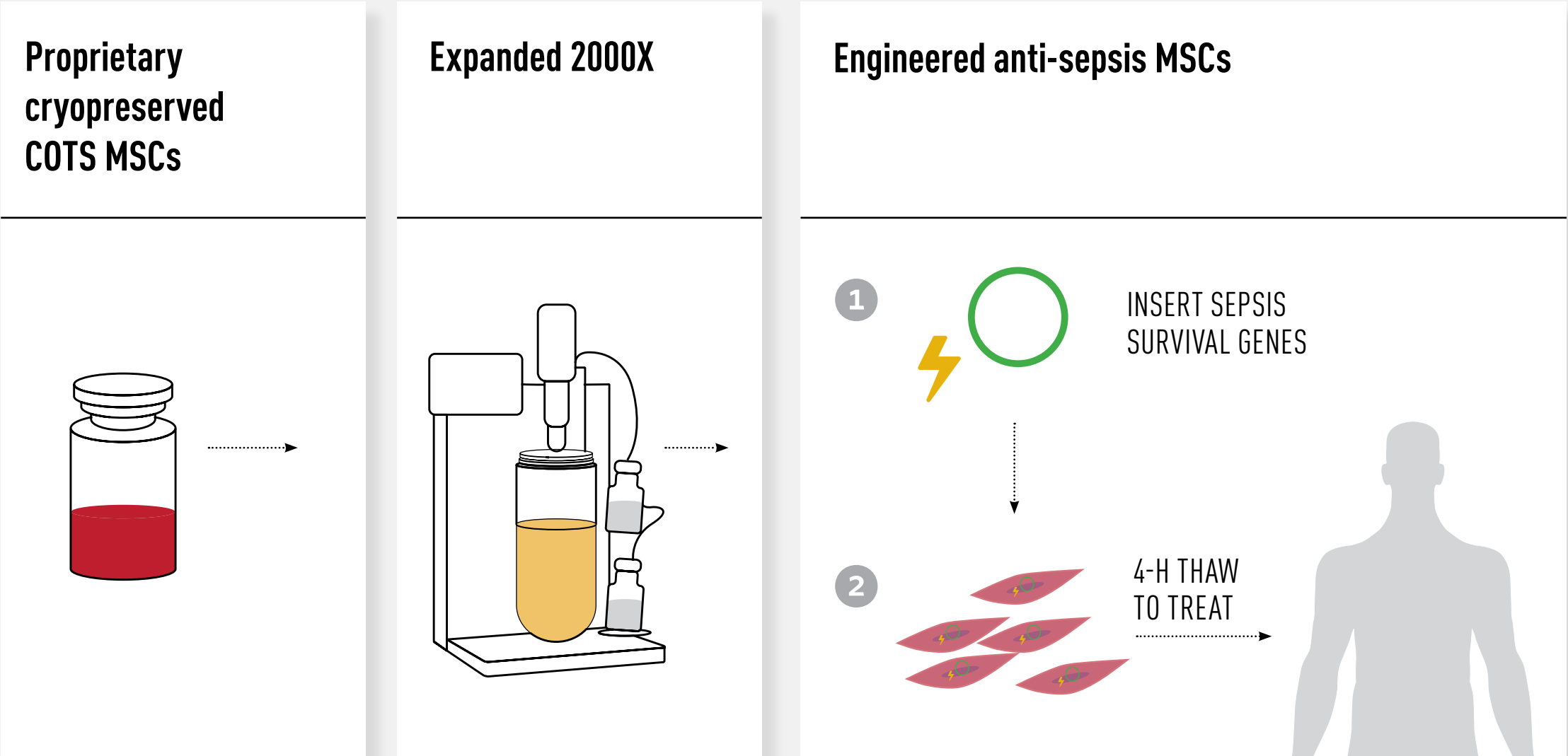
Bioreactor



Sepsis survival genes



MSC | Mesenchymal Stem Cell





POC: MSC THERAPY FOR SEPSIS

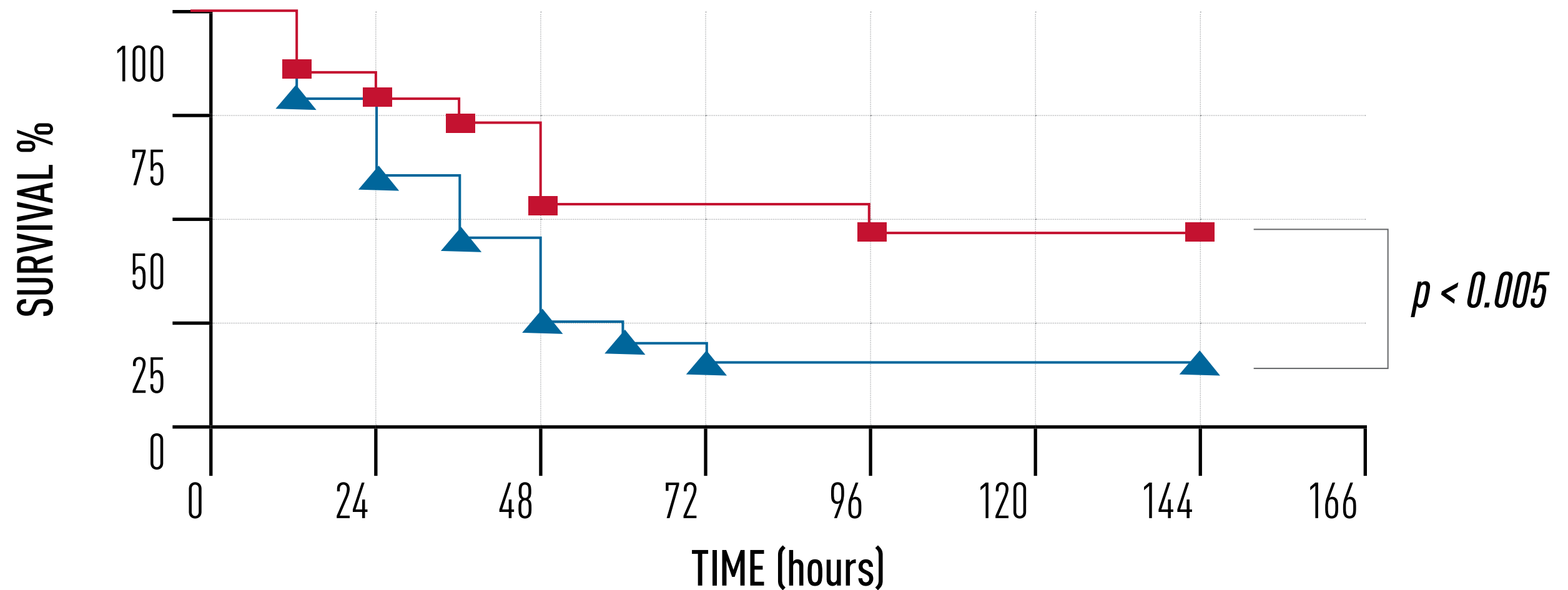
MESENCHYMAL STEM CELLS REDUCE INFLAMMATION WHILE ENHANCING BACTERIAL CLEARANCE AND IMPROVING SURVIVAL IN SEPSIS

Shirley H. J. Mei^{1,4*}, Jack J. Haitsma^{2*}, Claudia C. Dos Santos², Yupu Deng¹, Patrick F. H. Lai⁴, Arthur S. Slutsky^{2,4}, W. Conrad Liles^{3,4,5#}, and Duncan J. Stewart^{1,4#}

¹The Ottawa Hospital Research Institute, University of Ottawa, Ottawa; ²The Keenan Research Centre in the Li Ka Shing Knowledge Institute of St. Michael's Hospital and the Interdepartmental Division of Critical Care Medicine, University of Toronto; ³McLaughlin-Rotman Centre for Global Health, Toronto General Research Institute; ⁴Institute of Medical Science and ⁵Department of Medicine and McLaughlin Centre for Molecular Medicine, University of Toronto, Toronto, Ontario, Canada



CO-TREATMENT OF MSC AND ANTIBIOTICS → IMPROVED SURVIVAL OF SEPTIC ANIMALS BY 36%





LYING MICE VS. TRUTHFUL PATIENTS

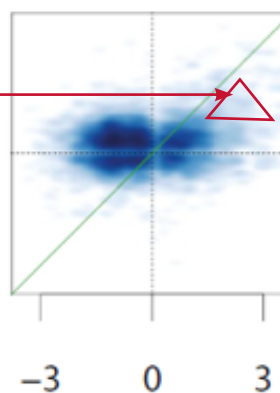
SEOK et al. GENOMIC RESPONSES IN MOUSE MODELS POORLY MIMIC HUMAN INFLAMMATORY DISEASES (PLOS 2013)

HUMAN SEPSIS

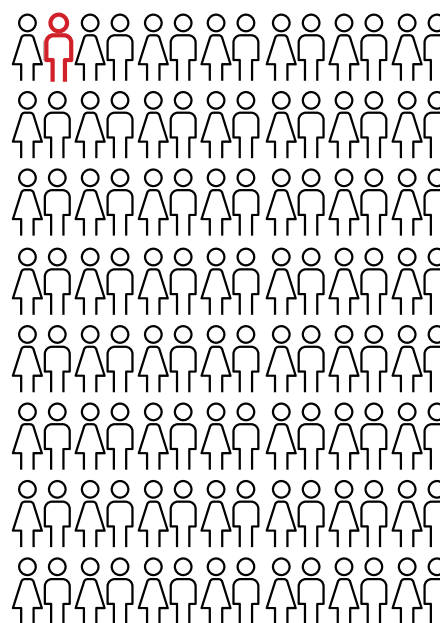
R .01

MOUSE SEPSIS

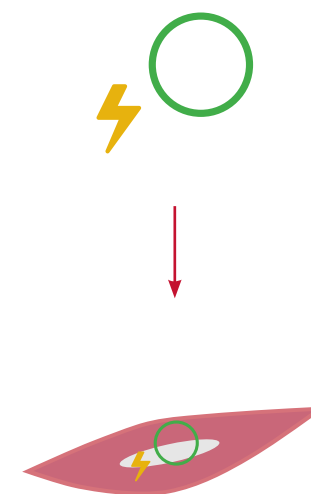
Rare mRNA found in both survivor mice and humans



1/160 septic patients have elevated survival protein with 65% lower mortality



Sepsis survival gene inserted into allogeneic MSCs



Aurora GT sepsis cells stored for treatment





**UTHR — FOCUSED
ON TODAY WHILE
BUILDING THE BRIDGES
TO FIND CURES**